Public Health Ontario
PARTNERS FOR HEALTH

Santé publique Ontario
PARTENAIRES POUR LA SANTÉ

Live attenuated influenza vaccine (LAIV) and inactivated influenza vaccines (IIV) for children: Information for health care providers on the 2016-2017 recommendations

October 2016

There have been recent changes in the recommendations for the live attenuated influenza vaccine (LAIV), (FluMist®, produced by MedImmune) for children and adolescents in both Canada and the United States. This fact sheet outlines these changes, the reasons for the changes, and the recommendations regarding LAIV and the inactivated influenza vaccine (IIV). It provides information for health care providers to support parents in their influenza vaccination decisions for their children.

Canadian Recommendations

Current Recommendation: The National Advisory Committee on Immunization (NACI) recommends that children 6 months up to and including 17 years of age receive a quadrivalent influenza vaccine. A quadrivalent vaccine is composed of two influenza A and two influenza B strains. Protection against the extra B strain in the quadrivalent vaccine compared to the trivalent vaccine is particularly important for children and adolescents, who are more likely to acquire influenza B than adults. As of August 2016, the quadrivalent influenza vaccine products recommended by NACI for children and adolescents are either:

- an injectable inactivated influenza vaccine (IIV) for children 6 months up to and including 17 years of age, or
- the live attenuated influenza vaccine (LAIV) given by nasal spray for children 2 years up to and including 17 years of age.[1]

Previous Recommendation*:* Prior to August 2016, NACI had preferentially recommended LAIV over IIV for children 2 years to under 6 years of age, and suggested that LAIV may also be more effective for children 6 years of age and over, but the exact age when it is no longer more effective in older children is not known.

U.S. Recommendations

Current Recommendation: In June 2016, the Advisory Committee on Immunization Practices (ACIP) in the United States made an interim recommendation that the live attenuated influenza vaccine (LAIV) not be used for the 2016-2017 influenza season.[2]

***Previous Recommendations**:* For the 2014-2015 influenza season, ACIP had made a preferential recommendation for LAIV over the inactivated influenza vaccine (IIV) for children 2 to 8 years of age. For the 2015-2016 influenza season, ACIP removed this preferential recommendation, stating that either LAIV or IIV could be used.

Why the recent changes in recommendations regarding the live attenuated influenza vaccine?

The concerns about the live attenuated influenza vaccine (LAIV) were first raised based on data from the 2013-2014 influenza season in the United States (U.S.). In that season, information from three U.S. vaccine effectiveness sentinel surveillance networks/studies found poor quadrivalent LAIV effectiveness against the circulating influenza A(H1N1)pdm09 strain. However, three Canadian studies from that season found that the trivalent LAIV performed as well as [3, 4] or better [5] than IIV (although one study had very few children receiving LAIV, making the results of this study less conclusive[3]).

Investigations in the U.S. suggested that the A(H1N1)pdm09 strain used to make LAIV may be particularly sensitive to inactivation by heat exposure.[6] Exposure to heat may occur in the U.S. when vaccines are shipped during the hotter summer months. As a result of these investigations, the manufacturer changed the A(H1N1)pdm09 strain in all of its LAIV from an A/California/7/2009(H1N1)pdm09-like strain to an antigenically similar strain, A/Bolivia/559/2013, which was believed to be more heat stable.[1]

However, in the 2015-2016 influenza season, with a predominance of the A(H1N1)pdm09 strain circulating, the U.S. again found poor vaccine effectiveness for quadrivalent LAIV against this strain in two of the three U.S. sentinel surveillance networks/studies. In these two studies, effectiveness against LAIV was lower than for IIV. Results from the third U.S. study, and studies from Canada and other countries where A(H1N1)pdm09 circulated in 2015-2016, showed higher vaccine effectiveness for quadrivalent LAIV against A(H1N1)pdm09 than found in the two U.S. studies. However, when assessing results from the third U.S. study and other countries, vaccine effectiveness for LAIV was somewhat lower than IIV (Please see Table 1 for details).

Why did Canada make a different recommendation than the U.S.?

The U.S. made an interim recommendation for 2016-2017 that the live attenuated influenza vaccine (LAIV) not be used. This was based on their experience with quadrivalent LAIV effectiveness against A(H1N1)pdm09 in 2013-2014 and 2015-2016. Switching the vaccine strain in LAIV from A/California to A/Bolivia in 2015 did not appear to rectify the low LAIV effectiveness against the A(H1N1)pdm09 strain. Canada did not have a problem with the effectiveness of the trivalent LAIV against A(H1N1)pdm09 in 2013-2014. In 2015-2016, vaccine effectiveness of quadrivalent LAIV against A(H1N1)pdm09 in Canada and other countries was higher than in the U.S.. Therefore, Canada recommends either the quadrivalent LAIV or inactivated influenza vaccines.

Why did Canada remove the preferential recommendation for the live attenuated influenza vaccine?

Previous preferential recommendations for live attenuated influenza vaccine (LAIV) over inactivated influenza vaccines (IIV) were based on three randomized controlled trials.[7, 8, 9] However recent studies have shown LAIV and IIV to have similar vaccine effectiveness against influenza A(H3N2) and B, and in some studies but not others, IIV performs somewhat better than LAIV against influenza A(H1N1)pdm09. Based on this information, the National Advisory Committee on Immunization (NACI) removed the preferential recommendation for LAIV over IIV.

Why is the live attenuated influenza vaccine showing lower vaccine effectiveness than the inactivated vaccine against A(H1N1)pdm09 in some studies, and working particularly poorly in the U.S. ?

As the name implies, LAIV is a live, weakened influenza vaccine that works by growing in the nasopharynx and inducing an immune response. In this way, it mimics the immune response induced by natural infection. Possible explanations for the lower vaccination effectiveness for LAIV against A(H1N1)pmd09 in some studies is that the vaccine strain is inhibited from growing in the nasopharynx because:

- it must compete with the three other strains that are part of the quadrivalent formulation; or
- past exposure to A(H1N1)pdm09 from either past vaccination or infection is inhibiting the growth of the vaccine strain in the nasopharynx.

It is uncertain why the live attenuated influenza vaccine (LAIV) is working particularly poorly against A(H1N1)pdm09 in the U.S.. Further research is ongoing in this area.

What does all this mean for Canadian and Ontario children and adolescents?

In Canada, the National Advisory Committee on Immunizations (NACI) recommends a quadrivalent vaccine for children 6 months up to and including 17 years of age. For children 6 months to under 2 years of age, only the inactivated influenza vaccine (IIV) is authorized. Children 2 years up to and including 17 years of age can receive either an IIV product or the live attenuated influenza vaccine (LAIV), as long as the child has no contraindications. Consistent with NACI's recommendation, Ontario offers quadrivalent IIV and LAIV for children and adolescents 2 years up to and including 17 years of age as part of its publicly-funded influenza immunization program.

Contraindications particular to LAIV include:

- Immunocompromised by disease or medication;
- Severe asthma or active wheezing;
- Taking long-term aspirin or aspiring-containing medication (because of the potential concern regarding Reye's syndrome);
- Pregnant;
- Taking an influenza antiviral medication (i.e., oseltamivir or zanamivir) in the preceding 48 hours.

For more details regarding contraindications for LAIV and IIV, please see:

- The 2016-2017 National Advisory Committee on Immunization (NACI) Influenza Statement
- The Ministry of Health and Long-Term Care fact sheet on Quadrivalent Influenza Vaccines

Note that egg allergy is no longer a contraindication for LAIV[10] and has not been a contraindication for IIV for a number of years.

In conclusion, in children and adolescents 2 years up to and including 17 years of age with no contraindications, either LAIV or IIV can be used, and the decision may come down to whether the child/adolescent prefers a nasal spray or a needle in their arm.

Additional Information

More information is available from your local public health unit, Public Health Ontario (cd@oahpp.ca) or the following sources:

- Public Health Ontario's Grand Rounds presentation: Influenza and Influenza Vaccine Updates (October 5, 2016)
- National Advisory Committee on Immunization (NACI). Canadian Immunization Guide Chapter on Influenza and Statement on Seasonal Influenza Vaccine for 2016-2017. Addendum – LAIV Use in Children and Adolescents. http://www.phac-aspc.gc.ca/naci-ccni/flu-2016-grippe-addendum-children-enfants-eng.php
- Grohskpof LA, Sokolow LZ, Broder K et al. Prevention and Control of Seasonal Influenza with Vaccines. Recommendations of the Advisory Committee on Immunization Practices — United States, 2016–17 Influenza Season. Morbidity and Mortality Weekly Report (MMWR) August 26, 2016 / 65(5);1–54 http://www.cdc.gov/mmwr/volumes/65/rr/rr6505a1.htm

General information about the Universal Influenza Immunization Program in Ontario is available on the Ministry of Health and Long-Term Care website.

Table 1

Summary of 2015-2016 vaccine effectiveness (VE) results for the quadrivalent live attenuated influenza vaccine (LAIV), including comparisons to the inactivated influenza vaccine (IIV) where available

Study	LAIV 4 VE	IIV VE
U.S. Flu Vaccine Effectiveness Network – CDC - U.S. [11, 12] A/H1N1pdm09; 2-17 years of age; adjusted analysis	-15% or -21% (Not statistically significant)	54% or 65% (Statistically significant)
Department of Defense dependents - U.S. [11] A/H1N1pdm09; 2-17 years of age	15% (Not statistically significant)	68% (Statistically significant)
Influenza Clinical Investigation for Children (ICICLE) - MedImmune – U.S. [13] A/H1N1pdm09; 2-17 years of age	50% (Not statistically significant)	71% (Statistically significant)
Sentinel Practitioner Surveillance Network (SPSN) – Canada [1] A/H1N1pdm09; age not specified	Approximately 50% (Not statistically significant)	Not provided
United Kingdom [14] A/H1N1pdm09; 2-17 years of age; adjusted analysis	41.5% (95% CI: -8.5 to 68.5)	100% (95% CI: 13.3 to 100)
Finland [15] Influenza A - A(H1N1)pmd09 predominated; 2 year olds; adjusted analysis	47.9% (95% CI: 21.6 to 65.4)	79.5% (95% CI: 50.3 to 91.6)

References

1. National Advisory Committee on Immunization (NACI). Canadian Immunization Guide Chapter on Influenza and Statement on Seasonal Influenza Vaccine for 2016-2017. Addendum – LAIV Use in Children and Adolescents. http://www.phac-aspc.gc.ca/naci-ccni/flu-2016-grippe-addendum-children-enfants-eng.php
2. Grohskopf LA, Sokolow LZ, Broder KR et al. Prevention and Control of Seasonal Influenza with Vaccines. Recommendations of the Advisory Committee on Immunization Practices — United States, 2016–17 Influenza Season. Morbidity and Mortality Weekly Report (MMWR) August 26, 2016;65(5):1–54. http://www.cdc.gov/mmwr/volumes/65/rr/rr6505a1.htm
3. Skowronski DM, Chambers C, Sabaiduc S et al., Integrated Sentinel Surveillance Linking Genetic, Antigenic, and Epidemiologic Monitoring of Influenza Vaccine-Virus Relatedness and Effectiveness During the 2013–2014 Influenza Season. Journal of Infectious Diseases (2015) 212 (5): 726-739 first published online March 17, 2015. http://jid.oxfordjournals.org/content/212/5/726.full.pdf+html
4. Loeb B, Russell ML, Manning V, et al Live Attenuated Versus Inactivated Influenza Vaccine in Hutterite Children: A Cluster Randomized Blinded Trial. Annals of Internal Medicine. Published online 16 August 2016. http://annals.org/article.aspx?articleid=2543271
5. Kwong JC, Pereira JA, Quach S et al. Randomized Evaluation of Live Attenuated vs. Inactivated Influenza Vaccines in Schools (RELATIVES) Cluster Randomized Trial: Pilot Results from a Household Surveillance Study to Assess Direct and Indirect Protection from Influenza Vaccination. Vaccine. 2015 September 11;33(38):4910-5. https://www.ncbi.nlm.nih.gov/pubmed/26232348
6. Cotter CR, Jin H, Chen Z. A Single Amino Acid in the Stalk Region of the H1N1pdm Influenza Virus HA Protein Affects Viral Fusion, Stability and Infectivity. PLoS Pathogens 2014. 10(1): e1003831. doi:10.1371/journal.ppat.1003831 http://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1003831#ppat-1003831-g004
7. Belshe RB, Edwards KM, Vesikari T et al. Live Attenuated Versus Inactivated Influenza Vaccine in Infants and Young Children. New England Journal of Medicine 2007;356:685-96.
8. Fleming DM, Crovari P, Wahn U et al. Comparison of the Efficacy and Safety of Live Attenuated Cold-Adapted Influenza Vaccine, Trivalent, with Trivalent Inactivated Influenza Virus Vaccine in Children and Adolescents with Asthma. Pediatric Infectious Disease Journal 2006; 25:860–869.
9. Ashkenazi S, Vertruyen A, Aristegui J et al., Superior Relative Efficacy of Live Attenuated Influenza Vaccine Compared with Inactivated Influenza Vaccine in Young Children with Recurrent Respiratory Tract Infections. Pediatric Infectious Disease Journal 2006; 25:870–879.
10. National Advisory Committee on Immunization (NACI). Canadian Immunization Guide Chapter on Influenza and Statement on Seasonal Influenza Vaccine for 2016-2017. Addendum - LAIV Use in Egg Allergic Individuals. http://www.phac-aspc.gc.ca/naci-ccni/flu-2016-grippe-addendum-eggs-oeufs-eng.php
11. Flannery B, Chung J. Influenza Vaccine Effectiveness, Including LAIV vs IIV in Children and Adolescents, US Flu VE Network, 2015-16. June 22, 2016 presentation at the Advisory Committee on Immunization Practice (ACIP) meeting. http://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2016-06/influenza-05-flannery.pdf

12. Flannery B. LAIV vs IIV effectiveness, Summary of evidence since 2000. June 22, 2016 presentation at the Advisory Committee on Immunization Practice (ACIP) meeting. http://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2016-06/influenza-07-flannery.pdf
13. Ambrose C. 2015-16 US Influenza Vaccine Effectiveness, Influenza Clinical Investigation for Children (ICICLE) Study. June 22, 2016 presentation at the Advisory Committee on Immunization Practice (ACIP) meeting. http://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2016-06/influenza-06-ambrose.pdf
14. Pebody R, Warburton F, Ellis J et al., Effectiveness of Seasonal Influenza Vaccine for Adults and Children in Preventing Laboratory-Confirmed Influenza in Primary Care in the United Kingdom: 2015/16 End-of-Season Results. Eurosurveillance, 22 September 2016 ;21(38). http://eurosurveillance.org/ViewArticle.aspx?ArticleId=22592
15. Nohynek H, Baum U, Syrjänen R, et al. Effectiveness of the Live Attenuated and the Inactivated Influenza Vaccine in Two-Year-Olds – A Nationwide Cohort Study Finland, Influenza Season 2015/16. Eurosurveillance 22 September 2016; 21(38). http://eurosurveillance.org/ViewArticle.aspx?ArticleId=22589

Public Health Ontario acknowledges the financial support of the Ontario Government.